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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,966	09/11/2003	Richard B. Roth	SEQ-4038-UT	9006

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GRANT ANDERSON LLP
C/O PORTFOLIOIP
PO BOX 52050
MINNEAPOLIS, MN 55402

EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,966	ROTH ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-14 and 49-53* is/are pending in the application.

4a) Of the above claim(s) *5-9,11,12 and 49-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-.07, 8-07, 3-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-9, 11-14, and 49-53 are pending in the instant application. Claims 5-9, 11-12 and 49-53 are withdrawn from consideration at this time as being drawn to non elected invention(s). Claims 1-4, and 13-14 are currently under examination. This office action is in response to the papers filed 3/19/2007, 5/28/2007. and 7/27/2007. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is NON-FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The rejection of claims 1, 2, 13, and 15, under 35 USC 102(e) as being anticipated by Stratton, is withdrawn in view of the amendments to the claims.

Compact Disc Submission

4. Portions of this application are contained on compact disc(s). When portions of an application are contained on a compact disc, the paper portion of the specification must identify the compact disc(s) and list the files including name, file size, and creation date on each of the compact discs. See 37 CFR 1.52(e). Compact disc labeled "CRF" is not identified in the paper portion of the specification with a listing of all of the files contained on the disc. Applicant is required to amend the specification to identify each disc and the files contained on each disc including the file name, file size, and file creation date.

5. This application contains compact disc(s) as part of the originally filed subject matter, but does not contain an incorporation by reference statement for the compact discs. See 37 CFR 1.77(b)(4). Applicant(s) are required to insert in the specification an incorporation-by-reference of the material on the compact disc(s).

6. NOTE: These requirements were made in the previous office action but have not been addressed in any of the responses filed.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-2, and 13-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to identifying a human subject at risk of melanoma comprising detecting the presence or absence of one or more polymorphic variations in an intron of a region between about the position of rs1267618 and about the position of rs1639679, whereby the presence of the one or more polymorphisms is indicative of the subject being at risk of melanoma.

The genus encompassed by the claims is a broad variable genus as discussed below. The claims encompass detection of any polymorphism in introns spanning over 80 kb of SEQ ID NO: 1, which the specification teaches is a BRAF nucleotide sequence, however the specification only teaches the identification of 12 SNPs in SEQ ID NO: 1 in humans (tables 7-10) which is over 190 kb. Of these 12, on genotype analysis, none are statistically associated with melanoma in females (table 10), and only 6 have a p value of less than 0.05 in males (table 9).

At page 68, the specification teaches that positions 146311 (rs1639679), 138875 (rs1267646), 76799 (rs1267606) and 68398 (rs1267621) in SEQ ID NO: 1 are in strong linkage disequilibrium. However, in table 9, only the SNP at position 146311 (rs1639679) has a p value of less than 0.05. The other three SNPs do not appear to be, based on single genotype analysis, associated with melanoma in males. None of the SNPS (table 10) appear to be associated with melanoma in females. Accordingly, the detection of a SNP within this region would not be predictably diagnostic of melanoma or risk of melanoma. It is clear from tables 9 and 10, that a SNP, by virtue of being in an intron in the claimed region is not necessarily associated with melanoma. The specification provides no structure/function correlation between any particular SNP in linkage disequilibrium with the elected SNP that is diagnostic for melanoma risk. Although the specification asserts "males having an adenine at position 146311 (rs1639679) of SEQ ID NO: 1 are predisposed to melanoma" (page 61, para 00213), as evidenced by the haplotypes at table 12, both the C and the A alleles occur in different genetic backgrounds. Additionally, the specification teaches that allelotyping failed at this position (table 7). Therefore, it is not clear that disease association for this SNP was validated at the genetic level (see page 61, para 00212, last sentence). The specification teaches that haplotypes CTTG and

ATGA (first position of haplotype is position 146311 (rs1639679)) are both associated with melanoma risk in males, but not females (tables 14 and 15). However, both the C and the A allele are also found in non risk associated haplotypes. Therefore, it is clear that determination of either the C or the A allele at position 146311 (rs1639679), alone, is not indicative of melanoma risk, in either males or females. However, the claims are broadly drawn to determination of a single position.

The current claims encompass detection in a large variable genus of nucleic acids which comprise polymorphisms in introns spanning over 80 kb of the BRAF gene. The genus includes an enormous number of polymorphisms and mutations for which no written description is provided in the specification. The specification only teaches of 12 particular polymorphisms for which data is provided. However, as noted above, the data for each SNP is conflicting in males vs females, as well as with genotype analysis of each positions singly. Thus, applicant has express possession of only 12 particular polymorphisms in SEQ ID NO: 1 which show conflicting association in melanoma, in a genus which comprises hundreds of millions of different possibilities.

The broad variable genus is not represented by the particularly 12 named variants in table 4 of the specification for the reasons which follow. In the broadly claimed invention, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with melanoma is provided. However, no predictable correlation between the structural alterations of the 12 polymorphisms disclosed and melanoma is provided by the

specification. The specification does not teach the function of polymorphisms of the BRAF "region" nor how their function, or lack of function, or altered function are predictably associated with melanoma. The specification teaches 12 SNPs (table 4) were found in SEQ ID NO: 1, but that only 6 particular positions exhibited a p value of less than 0.05, and the identity of any particular "risk associated" allele is unclear. The specification provides no guidance that broadly "any" polymorphism in the encompassed nucleic acids would be predictable of melanoma association. It is further noted that the claims broadly encompass "any" polymorphic variation at the disclosed position (eg, elected position 146311 (rs1639679) of SEQ ID NO: 1), but only teaches 2 out of 4 possible variations at each position (A/C at position 146311 (rs1639679)). The specification does not teach if a G or T would be statistically associated with melanoma nor does it provide any guidance as to whether the particular nucleotide variants even exist. The specification provides no guidance that any alteration is diagnostic for increased risk for melanoma.

Further, these claims expressly encompass allelic variants including insertions, deletions, substitutions and transversions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing additional sequence, which are associated with any phenotype are described in the specification. Additionally, the specification provides no evidence that any SNP at such position, in either humans, or mice or dogs for example, provides a predictable association with melanoma. The polymorphisms shown are not representative of the genus of any polymorphism associated with melanoma because it is not clear which polymorphisms within a BRAF region would have the same affect. It is not clear whether the polymorphisms shown are causative for the detected phenotype or whether they may simply

represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in the melanoma may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. Accordingly, the particularly disclosed variants are not representative of the large variable genus encompassed by the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and polymorphisms in view of the species disclosed. The skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention. However, Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with

reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

Response to Arguments

9. The responses dated 5/28/2007 and 7/27/2007 traverse the rejection. The responses as well as the declaration under 37 CFR 1.132 by Dr. Charles Cantor have been thoroughly reviewed but were not found persuasive to overcome the rejection. The response dated 5/28/2007 asserts that the concept of linkage disequilibrium in genetics embodies the phenomenon that a disease-associated region in the human genome contains a cluster of polymorphisms associated with a disease state and asserts that identifying multiple polymorphisms associated with a disease state also identifies a region associated with the disease state consistent with the concept of linkage disequilibrium, and cites a portion from "Cantor & Smith, Genomics, 1999, page 192, which states "markers very close to the disease gene will tend, more likely than average, to retain the haplotype of the original chromosome because, as the distance to the disease shrinks, it becomes less likely that recombination events have occurred in this particular region". The response further asserts that the specification analyzed several polymorphisms in the region of the human genome specified by claim 1 and identified several associated with melanoma. The response asserts that 10 polymorphisms where identified that were associated with melanoma with a p value of less than .05 of the 12 polymorphisms analyzed in the claimed region and thus have provided a written description for the claimed

subject matter because Applicant identified a region associated with melanoma by virtue of identifying several polymorphisms associated with melanoma in the claimed region. The response asserts that this is a representative number of polymorphic positions. The response also asserts that Applicant analyzed haplotypes within the claimed region and determined 4 variants were in strong LD. The response asserts that the fact that these 4 polymorphic variants are located at the termini of the claimed region and the finding of strong LD, provides evidence that the claimed region is significantly associated with melanoma. These arguments have been thoroughly reviewed but were not found persuasive.

With regard to the assertion that 10 polymorphisms were found with a p value of less than 0.05, it is noted that at para 00212, the specification states "When genotyping results agreed with the original alleletyping results, the SNP disease association was considered validated at the genetic level". Comparing the data in tables 7 and 9, it is shown that only 3 of the 12 SNPs had a p value less than 0.05 by both alleletyping and genotyping in males. No SNPs appear to be disease associated in females (see tables 8 and 10). Accordingly, it appears that disease association for only 3 of the 12 SNPs was validated at the genetic level in males only. At page 68, the specification teaches that positions 146311 (rs1639679), 138875 (rs1267646), 76799 (rs1267606) and 68398 (rs1267621) in SEQ ID NO: 1 are in strong linkage disequilibrium. None of these correspond to the 3 SNPs validated at the genetic level. Further, in table 9, only the SNP at position 146311 (rs1639679) has a p value of less than 0.05. The other three SNPs do not appear to be, based on single genotype analysis, associated with melanoma in males. None of the SNPS (table 10) appear to be associated with melanoma in females. Accordingly, the detection of a SNP within this region would not be predictably diagnostic of melanoma or risk of

melanoma. It is clear from tables 9 and 10, that a SNP, by virtue of being in an intron in the claimed region is not necessarily associated with melanoma. The specification provides no structure/function correlation between any particular SNP in linkage disequilibrium with the elected SNP that is diagnostic for melanoma risk. Although the specification asserts "males having an adenine at position 146311 (rs1639679) of SEQ ID NO: 1 are predisposed to melanoma" (page 61, para 00213), as evidenced by the haplotypes at table 12, both the C and the A alleles occur in different genetic backgrounds. Additionally, the specification teaches that allelotyping failed at this position (table 7). Therefore, it is not clear that disease association for this SNP was validated at the genetic level (see page 61, para 00212, last sentence). The specification teaches that haplotypes CTTG and ATGA (first position of haplotype is position 146311 (rs1639679)) are both associated with melanoma risk in males, but not females (tables 14 and 15). However, both the C and the A allele are also found in non risk associated haplotypes. Further, H1 has a frequency of .843, however while every position is varied in H2 while the T at position 138875 is varied in H4. It is clear from the number of different haplotypes in table 12, that despite the specification's assertion regarding strong LD, a large number of different haplotypes exist, where the alleles at the 4 indicated positions are not necessarily correlative of each other. From the data in table 12, it is appears that the determination of either the C or the A allele at position 146311 (rs1639679), alone, is not indicative of melanoma risk, in either males or females. However, the claims are broadly drawn to determination of a single position.

The declaration by Dr. Charles Cantor, at section 3, asserts that the patent application presents a genomic study in which many SNPs spaced throughout the entire genome were typed in two populations, a melanoma population and a "healthy" control population., where regions

that contained multiple disease associated polymorphisms were verified as being statistically associated with melanoma, on region encoding the BRAF protein. The declaration asserts that several polymorphisms were typed in this region, several of which were spaced across the studied region and that "the inventors identified that the BRAF region was significantly associated with melanoma. At section 4, the declaration reiterates arguments with regard to LD made in the response dated 5/28. At section 7, the declaration reiterates arguments made in the response dated 5/28 with regard to the specific haplotypes taught in table 12 and the large sample size. These arguments have been thoroughly reviewed but were not found persuasive. The office action does not question the methodology used by applicants to arrive at a region that warranted further study to determine melanoma disease association. However, while these methods can identify a region that warrants further study, it does not provide a description of a representative number of specific alleles within the region which are disease associated vs not. This is exemplified by the conflicting data in tables 7-10 of the specification. Of 12 SNPs identified by applicants in the "hot zone", only 3 were validated at the genetic level as being disease associated, none of which are the 4 SNPs in the disease asserted haploytpes in table 12 which were found to be in "strong" LD. Further, the fact that polymorphic positions may be found to be in strong LD with each other, it is clear that despite such , the alleles are not necessarily correlative of each other. H1 is taught to have a frequency of 0.843, however while every position is varied in H2, only the T at position 138875 is varied in H4. Yet, both H2 and H4, which only have a single allele in common, are taught to be disease associated. The value of each individual position as a disease associated marker is unclear, however, as the entire human population would be expected to have either allele. It is clear from the number of different

haplotypes in table 12, that despite the specification's assertion regarding strong LD, a large number of different haplotypes exist, where the alleles at the 4 indicated positions are not necessarily correlative of each other. From the data in table 12, it is appears that the determination of either the C or the A allele at position 146311 (rs1639679), alone, are not necessarily informative of melanoma risk, in males, and further given the data in tables 8 and 10, are not informative of disease risk in females. However, the claims are broadly drawn to determination of a single position.

At section 5, the declaration provides citations of several references as a showing that "identifying a disease associated region by this methodology is supported by the work of other researchers". This argument has been thoroughly reviewed, however the claims are not drawn to methods of identifying disease associated regions, but rather to identifying a human subject at risk of melanoma by detecting the presence of any specific polymorphic variation within the region. As already noted above, in the instant specification, only 6 of the 12 SNPs had a p value of less than 0.05 in males (table 9), while only 3 of the 12 SNPs appear to have been validated at the genetic level in males (see tables 7 and 9). Further, 3 of the SNPs in the "disease associated" haplotypes do not appear to be statistically associated with melanoma as exemplified by the data in table 9 in males, while none are associated in females. With regard to the references cited, while whole genome scanning methods were used to identify a CFH region associated with AMD, the references do not teach that based on this data, the skilled artisan would be able to determine which polymorphic variants are disease associated. For example, there are currently 566 SNPs in the CFH gene region taught in NCBI, however, Hageman only discusses haplotypes with 8 SNPs.

At section 6, the declaration asserts that the inventors typed a significant number of polymorphisms in the BRAF region in the process of determining that the region was associated with melanoma, and more specifically, 23% of the polymorphisms currently in the HapMap database having a minor allele frequency of greater than 0.5 in the claimed region. The declaration asserts that the inventors therefore have analyzed a significant number of polymorphisms. This argument has been thoroughly reviewed but was not found persuasive as the SNPs analyzed provide no indication as to which of the additional polymorphic variants identified after the invention was filed, are disease associated vs not. The Board in Ex parte Kubin 83 USPQ2d 1410 (Bd. Pat. App. & Int 2007), citing *Eli Lilly*, 119, F.3d at 1568, 43 USPQ2d at 1406, held that, sufficient description to show possession of a genus "may be achieved by means of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." The specification provides no structure/function relationship nor any additional identifying characteristics which would allow the skilled artisan to determine which of the additional SNPs are within the genus of "melanoma associated" SNPs. The Board additionally held that "Possession may not be shown by merely describing how to obtain possession of members of the claimed genus", citing *University of Rochester*, 358 F. 3d at 927, 69 USPQ2d at 1895. Although the specification teaches how to test other SNPs for disease association, it has not described which specific variations are disease associated vs not, within the genus. Without a correlation between structure and function, the claim does little more than define the claimed inventions by function.

Accordingly, the assertions made in the response dated 7/27/2007, page 2, last para to page 3, are not found persuasive.

The SNPs taught in the specification do not appear to be representative of the claimed genus. Therefore, given the conflicting data in the specification, as well as the post filing art of Jackson (Cancer Epidemiology, Biomarkers & Prevention, vol. 14, pages 913-918, 2005), which specifically teaches that no difference in the prevalence of the rs1639679 polymorphism associated with the H2 haplotype was found between cases and controls, it does not appear that the specification teaches a representative number of polymorphic variants that fall within the genus of disease associated polymorphisms encompassed by the claims. For these reasons, and the reasons made of record in the previous office action, the rejection is maintained.

10. Claims 1-4, and 13-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of

those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to identifying a human subject at risk of melanoma comprising detecting the presence or absence of one or more polymorphic variations in an intron of a region between about the position of rs1267618 and about the position of rs1639679, whereby the presence of the one or more polymorphisms is indicative of the subject being at risk of melanoma. The claims additionally recite methods wherein the one or more polymorphic variations comprises a polymorphic variation at rs1639679.

The nature of the claimed invention, therefore, requires the knowledge of predictive associations between any polymorphism in any of the recited nucleic acids.

The amount of direction or guidance and presence/absence of working examples:

The specification teaches that SEQ ID NO: 1 is a BRAF a nucleotide sequence (page 3). However, the specification does not teach which portions of SEQ ID NO: 1 are directed to the human BRAF gene, where the regulatory regions, such as the promoter, lie, and whether the sequence comprises the entire gene. The specification teaches that 12 polymorphisms were identified in the sequence (table 4) and teaches that allelotyping and genotyping analysis was conducted on Caucasian male and female subjects of German maternal and paternal descent (page 61). The specification teaches that analysis was undertaken for male and female cases with melanoma and for male and female controls not having cancer. The specification teaches

that when allelotyping and genotyping results agreed, the SNP disease association was considered validated at the genetic level (page 61).

The specification only teaches the identification of 12 SNPs in SEQ ID NO: 1 in humans (tables 7-10) which is over 190 kb. Of these 12, on genotype analysis, none were found to be statistically associated with melanoma in females (table 10), and only 6 have a p value of less than 0.05 in males (table 9). At page 68, the specification teaches that positions 146311 (rs1639679), 138875 (rs1267646), 76799 (rs1267606) and 68398 (rs1267621) in SEQ ID NO: 1 are in "strong" linkage disequilibrium. However, in table 9, only the SNP at position 146311 (rs1639679) has a p value of less than 0.05. The other three SNPs do not appear to be, based on single genotype analysis, associated with melanoma in males. None of the SNPS (table 10) appear to be associated with melanoma in females. Accordingly, the detection of a SNP within this region would not be predictably diagnostic of melanoma or risk of melanoma. It is clear from tables 9 and 10, that a SNP, by virtue of being in an intron in the claimed region of SEQ ID NO: 1 is not necessarily associated with melanoma. The specification provides no structure/function correlation between any particular SNP in linkage disequilibrium with the elected SNP that is diagnostic for melanoma risk. Although the specification asserts "males having an adenine at position 146311 (rs1639679) of SEQ ID NO: 1 are predisposed to melanoma" (page 61, para 00213), as evidenced by the haplotypes at table 12, both the C and the A alleles occur in different genetic backgrounds. Although the specification asserts "males having an adenine at position 146311 (rs1639679) of SEQ ID NO: 1 are predisposed to melanoma" (page 61, para 00213), as evidenced by the haplotypes at table 12, both the C and the A alleles occur in different genetic backgrounds. Additionally, the specification teaches that

allelotyping failed at this position (table 7). Therefore, it is not clear that disease association for this SNP was validated at the genetic level (see page 61, para 00212, last sentence). The specification teaches that haplotypes CTTG and ATGA (first position of haplotype is position 146311 (rs1639679)) are both associated with melanoma risk in males, but not females (tables 14 and 15). However, both the C and the A allele are also found in non risk associated haplotypes. Therefore, it is clear that determination of either the C or the A allele at position 146311 (rs1639679), alone is not indicative of melanoma risk, in either males or females.

The specification provides no universal correlation that any SNP in the claimed region would be associated with melanoma nor does it provide any way to predict which sequences within the broadly claimed sequences would be "melanoma associated". Of 12 disclosed SNPs, the specification teaches a p value of less than 0.05 in 6 positions, in males only. Thus it is clear that "any" polymorphism in the encompassed nucleic acids would not be predictable of melanoma risk.

Additionally, the specification provides no guidance as to how the SNP at 146311 (rs1639679) (A/C), or any of the other 11 variants, singly or in haplotypes, function to provide for increased risk of melanoma. The specification provides no structure/function correlation between the disclosed SNPs and melanoma for the skilled artisan to be able to predict which other positions within the claimed regions might be predictably associated with the claimed phenotypes. The elected allele could be part of a melanoma-associated haplotype, however the causative mutation is not necessarily one of the SNPs taught in the specification. The causative mutation could be in a gene thousands of nucleotides away, however the specification provides no indication of what this allele might be.

The specification provides no predictable association that any alteration, in the claimed regions of the BRAF gene in humans is diagnostic for increased risk of melanoma. No common element or attributes of the sequences are disclosed which would permit selection of sequence polymorphisms as diagnostic for an increased risk of melanoma. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with melanoma is provided. Further, these claims expressly encompass allelic variants including insertions, deletions, substitutions and transversions at thousands of different sites. However, the specification provides no evidence that any polymorphic variation at such positions in humans, provides a predictable association with melanoma. The polymorphisms shown are not predictive of the genus of any polymorphism associated with melanoma because it is not clear which polymorphisms within the claimed regions would have the same affect. It is not clear whether the polymorphisms shown are causative for the detected phenotype or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in the detected melanoma association may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. The specification does not teach the function of polymorphisms of SEQ ID NO: 1, nor how their function, or lack of function, or altered function are predictably associated with melanoma.

The state of the prior art and the predictability or unpredictability of the art:

At the time the invention was filed, the prior did not teach the function or biological activity of polymorphisms in BRAF with regard to melanoma. The specification demonstrates

the unpredictability of this invention since 6 of the 12 identified SNPs in SEQ ID NO: 1 were not statistically significant in males and none of the 12 were statistically significant in females, as well as the number of haplotypes which are not statistically significant in males or females, and do not appear to be melanoma associated given the data in the specification. Thisted et al (see galston.uchicago.edu/~thisted/, pages 1-5) notes that "It has become scientific convention to say that p-values exceeding .05 (one in twenty) just aren't strong enough to be the sole evidence that two treatments being studied really differ in their effect (see page 5).

Further, there is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. However, the art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. For example, Hacker et al. teaches that they were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Hacker et al; Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281 (5384):1787-1789).

With regard to BRAF, Laud (Laud et al; Cancer Research, vol. 63, pages 3061-3065; 2003) teaches that BRAF is unlikely to be a melanoma susceptibility gene. Laud teaches screening at the germline level for mutations in independent melanoma prone families, and patients with multiple primary melanoma without a familial history (see abstract). Laud teaches that 13 variants were identified, including 4 which were silent and 9 which occurred in introns. Laud teaches that none of the variants segregated with melanoma in the 11 melanoma families studied and that there was no significant difference in the frequency of heterozygotes for BRAF variants between melanoma and controls. Further, Jackson (Jackson et al; Cancer Epidemiology, Biomarkers, and Prevention; vol. 14, 2005, pages 913-918) teaches that somatic mutations of BRAF had been identified in both melanoma tumors and benign nevi, but that germ line mutations had not been identified as causal in families predisposed to melanoma (see abstract). Jackson teaches that a recent study (referring to Meyer et al; Journal of Carcinogenesis, vol 2, 2003, pages 1-5, which appears to teach portions of the data in the instant specification) suggested that a BRAF haplotype was associated with risk of sporadic melanoma in men (see abstract). Jackson teaches that this observation needed to be assessed in another population. Jackson teaches screening a 1 KB region upstream of the BRAF start codon, which is thought to contain the promoter, for variants (page 913, col 2, 2nd full para). Jackson teaches 6 variants were found and that a promoter insertion/deletion, which is in linkage disequilibrium with the intron 11 SNP (rs1639679) at position 146311 (rs1639679) of SEQ ID NO: 1, was analyzed in populations from the UK, for melanoma susceptibility, but that no statistically significant difference in either genotype or allele frequencies between cases and controls overall or between male and female cases was found (see abstract). Further, Jackson teaches that there was "no

difference in the prevalence of the intron 11 polymorphism [position 146311 (rs1639679) of SEQ ID NO: 1] associated with the H2 haplotype between cases and controls" and that "no difference as seen in the familial cases, where there was a higher allele frequency in males compared with females. This result is only just significant (P=0.05) and may be due to chance, especially as the allele frequency estimated from the female familial cases is the lowest of the sample series that we studied (table 3). In addition, we have found no evidence for an association between a common promoter insertion/deletion (present in the haplotype H2 described by Meyer) and melanoma risk". Accordingly, the art confirms the unpredictability of associating SNPs, including those in BRAF and including those in linkage disequilibrium, with disease susceptibility including in different populations, even for SNPs which have been found to be associated in other studies.

In the instant case, the specification only provides information that the A/C variant exists in humans and is associated with melanoma in certain haplotypic backgrounds in males only, but provides no guidance that it, or any other alleles which either are or are not in linkage disequilibrium, in SEQ ID NO: 1, have any effect whatsoever on the expression or activity of human BRAF or the broadly claimed sequences.

The level of skill in the art:

The level of skill in the art is deemed to be high, however the experimentation required to practice the broadly claimed invention is even higher.

The quantity of experimentation necessary:

The quantity of experimentation in this area is extremely large as it requires analysis of individual positions in the claimed region to determine whether any alteration at each position is associated with melanoma and to identify which variations are predictably associated with melanoma in any human subject. As neither the art nor the specification provide guidance as to which alterations at positions throughout BRAF are predictably associated with melanoma, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable. Screening each possible alteration in the broadly claimed genomic sequences, represents an inventive and unpredictable undertaking in itself, with each of the many intervening steps, not providing any guarantee of success.

In order to practice the invention as claimed, one would first have to establish that a predictive relationship exists between the disclosed polymorphisms and melanoma. Further, the scope of many of the claims requires knowledge of an association between all mutations in the claimed BRAF gene regions and melanoma in humans. Due to the scope of the claims, one of skill in the art would be required to further undertake extensive trial and error experimentation with a large number of patients with melanoma and controls, to determine mutations that share a predictive correlation with melanoma.

Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

Response to Arguments

11. The response traverses the rejection. The response asserts that the specification identifies a region specified in claim 1 as associated with occurrence of melanoma and assert that applicants finding paves the way toward identifying and using polymorphisms of this region and asserts that the finding that the region specified in claim 1 guides the person of ordinary skill in the art toward routinely identifying any other polymorphisms associated with melanoma in that region. This response has been thoroughly reviewed but not found persuasive. Associating polymorphisms with a disease is not routine experimentation as the specification provides no predictable means to determine which of the additional SNPs within the claimed region (see Cantor declaration) are associated with melanoma. Additionally, the post filing date art of Jackson, as well as the conflicting data in the specification illustrate that merely screening a population for disease association is not routine, but requires unpredictable trial and error analysis.

The response asserts that the specification provides multiple working examples in support of the claimed subject matter and routine experimentation does not preclude a finding of enablement. The response asserts that the specification provides clear guidance for performing multiple types of methods useful for identifying polymorphisms associated with melanoma, and that the person of ordinary skill in the art could apply these methods in a routine manner to intronic polymorphisms specified by claim 1. This argument has been thoroughly reviewed but was not found persuasive. The working examples in the specification demonstrate the unpredictable nature of the claimed invention. For example, of 12 SNPs identified by applicants in the "hot zone", only 3 were validated at the genetic level as being disease associated, none of which are the 4 SNPs in the disease asserted haploytpes in table 12 which were found to be in

"strong" LD. Further, the fact that polymorphic positions may be found to be in strong LD with each other, it is clear that despite such, the alleles are not necessarily predictive of each other. H1 is taught to have a frequency of 0.843, however while every position is varied in H2, only the T at position 138875 is varied in H4. Yet, both H2 and H4, which only have a single allele in common, are taught to be disease associated. The value of each individual position as a disease associated marker is unclear, however, as the entire human population would be expected to have either allele. It is clear from the number of different haplotypes in table 12 that despite the specification's assertion regarding strong LD, a large number of different haplotypes exist, where the alleles at the 4 indicated positions are not necessarily predictive of each other. From the data in table 12, it is appears that the determination of either the C or the A allele at position 146311 (rs1639679), alone, are not necessarily informative of melanoma risk, in males, and further given the data in tables 8 and 10, are not informative of disease risk in females. Further, 3 of the SNPs in the "disease associated" haplotypes do not appear to be statistically associated with melanoma as exemplified by the data in table 9 in males, while none are associated in females.

The response asserts that the CAFC found enablement in *In re Wands* are applicable to the same finding of enablement here. The response asserts that the technology in Wands is similar to the technology described in the present specification in the sense that the person of ordinary skill in the art is prepared to screen additional polymorphisms in the region specified by claim 1. This argument has been thoroughly reviewed but not found persuasive. The claims are not drawn to a screening assay. The claims are drawn to a method of identifying a subject at risk of melanoma and the claims require the knowledge that a specific polymorphism is associated with melanoma. The claims do not recite a method of screening polymorphisms to determine if

the polymorphism is associated with melanoma The response asserts that the high level of skill in the art leads to the conclusion that any experimentation associated with the full claim scope is routine and not undue. However, as set forth above, associating any polymorphisms within the claimed region of the human genome is unpredictable experimentation and is undue, as exemplified by the conflicting data in the specification and the art. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

12. Claims 1-4, and 13-14 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The nucleotide sequence surrounding and comprising the position of rs1267618 and about the position of rs1639679 is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). Applicant refers in the claims and the specification of "region between about the position of rs1267618 and about the position of rs1639679" to give contextual reference for polymorphisms disclosed in the specification and in claims 1-4.

MPEP 608.01 (p)[R-2] teaches that "While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention."

The recitation of the rs numbers refers to a database and constitutes an attempt to incorporate by reference the subject matter which is contained within the recited records. This recitation constitutes an improper incorporation by reference of essential material since it is

material that is necessary to describe the claimed invention. Essential material may not be incorporated by reference to non-patent publications (MPEP 608.01)(p).

Therefore, the claims are rejected for failure to comply with the enablement requirement because the specification fails to provide essential subject matter for the practice of the claimed invention.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-4 and 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase "about the position of rs1267618 and about the position of rs1639679" to indicate a region from BRAF, however neither the claims nor the specification provide an indication as to what the metes and bounds of "about rs1267618" or "about rs1639679". For example, it is not clear if the boundary refers to sequences disclosed in dbSNP for each rs #. Accordingly, the metes and bounds of intronic regions encompassed by the claimed recitation is unclear.

Claim 1 is indefinite in the recitation of "presence or a absence of a polymorphic variation... in an intron of a region between... and about the position of rs1639679" because is not clear what the actual polymorphic variation is, in other words, is the variant the C or A at that position? The designation of rs1639679 is indicative of a specific nucleotide position in BRAF being polymorphic, however both dbSNP and the specification indicate the possible alleles (C/A) at that position. However neither define what the "variant" is. Further, given that both the C and

the A allele occur in haplotypes that the specification asserts is polymorphic, it is not clear what the "variant" allele is. It does not appear that one would be able to identify a subject as being at risk of melanoma simply by detecting that position rs1639679 is polymorphic, but rather by detecting the presence of a specific allele. However, the claim does not make clear what that allele is. This same issue exists for other rs #'s as well as the dependent claims which refer to an rs #.

Claim Rejections - 35 USC § 102

15. Claims 1-4 and 13 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. This is an inquiry under 35 USC 102(f). There appears to be an inconsistency as Myer et al (Journal of Carcinogenesis, vol. 2, 2003, pages 1-5), teaches the at risk alleles and haplotypes taught in the instant specification in humans in BRAF, as well as melanoma disease risk in men, in a Caucasian population of German descent (page 4), as well as methods of detecting polymorphisms in claim 13 (page 4, col. 2). The data in the specification and that in the paper appear to be the same. However, the inventorship of the instant application and the authorship of the paper are entirely different. MPEP 2137 states: "...it is incumbent upon the inventors named in the application, in reply to an inquiry regarding the appropriate inventorship under subsection (f), ...to provide a satisfactory showing by way of affidavit under 37 CFR 1.132 that the inventorship of the application is correct in that the reference discloses subject matter invented by the applicant rather than derived from the author or patentee notwithstanding the authorship of the article or the inventorship of the patent. *In re Katz*, 687 F.2d 450, 455, 215 USPQ 14, 18 (CCPA 1982) (inquiry is appropriate to clarify any ambiguity

created by an article regarding inventorship, and it is then incumbent upon the applicant to provide "a satisfactory showing that would lead to a reasonable conclusion that [applicant] is the...inventor" of the subject matter disclosed in the article and claimed in the application).

Response to Arguments

16. The response traverses the rejection and asserts that applicant does not believe there is an inconsistency between the invention designated in the subject patent application and reiterates the "Aknowledgements" section of the Myer et al reference. The response further asserts that the inventions developed the claimed subject matter and asserts "the undersigned understands that Mr. Myer's involvement was limited to providing nucleic acid samples at the request of the named inventors", and that "the remaining authors of the Myer document had no involvement with development of the claimed methods, other than possibly having an involvement with the nucleic acid samples". These arguments have been thoroughly reviewed but were not found persuasive. First, as already set forth above and in the previous office action: MPEP 2137 states: "...it is incumbent upon the inventors named in the application, in reply to an inquiry regarding the appropriate inventorship under subsection (f), ...to provide a satisfactory showing by way of affidavit under 37 CFR 1.132 that the inventorship of the application is correct in that the reference discloses subject matter invented by the applicant rather than derived from the author or patentee notwithstanding the authorship of the article or the inventorship of the patent. *In re Katz*, 687 F.2d 450, 455, 215 USPQ 14, 18 (CCPA 1982). No such affidavit has been filed by the inventors to rebut the inquiry set forth above. Second, as also noted in the MPEP 2137.01 II: "The definition for inventorship can be simply stated: 'The threshold question in determining inventorship is who conceived the invention. Unless a person contributes to the conception of the

invention, he is not an inventor.'" Although the response sets forth that the named inventors "developed" the claimed subject matter, the response does not make clear who conceived of the invention. From the arguments made in the response it is not clear if the genome wide screen is sufficient to show conception. For example, the response asserts that "the undersigned understands at this time that the named inventors 1. identified the claimed method for development", however it is not clear if this refers to general genome wide scans that applicants provide as a service to customers or if it pertains to the actual conception of "identifying a subject at risk of melanoma... comprises detecting the presence or absence of one or more polymorphic variations associated with melanoma in a nucleic acid sample from a human subject, wherein the polymorphic variation is detected in an intron of a region between about the position of rs1267618 and about the position of rs1639679...". The rejection is therefore maintained.

17. Claims 1, 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by dbSNP rs1639679 (publicly available in build 89, November 15, 2000).

rs1639679 teaches the detection of polymorphic alleles C/A (G/T in reverse complement) in homo sapiens. Although the claims are directed to identifying a subject at risk of melanoma, it is noted that the claims are directed to detecting the presence or "absence" of a polymorphic variation, which depending on the haplotype, appears to be either the C or A allele. There is no active step relating back to the preamble relating to the "absence" of the polymorphic variation, accordingly, the claims have been broadly interpreted to encompass detecting the "absence" of the variation.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 1-4, 13, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over rs1639679 in view of Soderlund (Soderlund et al; US Patent 6,013,431).

rs1639679 teaches polymorphic alleles C/T (G/A reverse complement) in homo sapiens. Although the claims are directed to identifying a subject at risk of melanoma, it is noted that the claims are directed to detecting the presence or "absence" of a polymorphic variation, which depending on the haplotype, appears to be either the C or A allele. There is no active step relating back to the preamble relating to the "absence" of the polymorphic variation, accordingly, the claims have been broadly interpreted to encompass detecting the "absence" of the variation.

rs1639679 does not specifically teach any particular method of detection, obtaining a nucleic acid sample from the subject, or hybridizing an oligonucleotide to the nucleic acid sample, wherein the oligonucleotide is complementary to the nucleotide sequence and hybridizes

to a region adjacent to the polymorphic variation, extending the oligonucleotide in the presence of one or more nucleotides yielding extension products and detecting the absence of the polymorphic variation in the extension products, or an oligonucleotide consisting of SEQ ID NO: 45, however Soderlund teaches methods of detecting specific nucleotide variations in the nucleic acid sample of a subject by hybridizing an oligonucleotide to the nucleic acid sample, wherein the oligonucleotide is complementary to the nucleotide sequence and hybridizes to a region adjacent to the polymorphic variation, extending the oligonucleotide in the presence of one or more nucleotides yielding extension products and detecting the absence of the polymorphic variation in the extension products (see abstract, figures 1-3, col. 8). Further, the sequence of SEQ ID NO: 45, is immediately adjacent to the polymorphic position set forth in rs1639679. Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to determine the identity of the polymorphism at rs1639679 using the methods of Soderlund because Soderlund teaches that such methods are suitable for identifying the allele of a polymorphic position. In carrying out the method of Soderlund to determine the allele at rs1639679, the skilled artisan would be motivated to generate appropriate oligonucleotides, including SEQ ID NO: 45, to detect the allele as taught by Soderlund.

Conclusion

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and

on alternate Fridays. NOTE: The examiner will be on maternity leave for a portion of December 2007, as well as the months of January and February 2008.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Jehanne Sitton/
Primary Examiner
Art Unit 1634
11/26/2007